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The role of RSV seasonality on RSV prevention strategy planning for passive immunisation of infants in low- and middle-income countries: a modelling study

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Abstract

Background: Respiratory syncytial virus (RSV) represents a substantial burden of disease in young infants in low- and middle-income countries (LMICs). As RSV passive immunisations, including maternal vaccine and monoclonal antibody (mAb), can only grant a temporary period of protection, their effectiveness and efficiency will be determined by the timing of the immunisation relative to the underlying RSV seasonality. We aimed to assess the potential impact of different approaches for passive RSV immunisations of infants in LMICs.

Methods: We selected 52 LMICs based availability of RSV seasonality data and developed a mathematical model to compare the impact of different RSV passive immunisation approaches (seasonal vs year-round approach). For each candidate approach, we calculated the expected annual proportion of RSV incidence among infants <6 months averted (effectiveness) and the ratio of per-dose cases averted between that approach and the year-round approach (relative efficiency).

Results: Most LMICs (39/52, 75%) had clear RSV seasonality, defined as having more than 75% of annual RSV cases occurring in ≤ 5 months. In these countries with clear RSV seasonality, the seasonal approach in which mAb administration began three months before the RSV season onset was only 16% less effective in averting RSV-associated acute lower respiratory infection (ALRI) hospitalisations than a year-round approach (Interquartile range, IQR: 13–18), but was 70% more efficient (IQR: 50–97); the seasonal approach that delivered maternal vaccination one month before the season onset was 27% less effective in averting RSV-ALRI hospitalisations than a year-round approach (IQR: 25–33), but was 126% more efficient (IQR: 87–177).

Interpretation: In LMICs with clear RSV seasonality, seasonal approaches to mAb and maternal vaccine administration might optimise disease prevention by dose given compared with year-round administration. More data are needed to clarify if seasonal administration of RSV mAb and/or maternal immunisation is programmatically suitable and cost-effective in LMICs.

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Research in Context

Evidence before this study

Respiratory syncytial virus (RSV) represents a substantial burden of disease in infants <6 months old in low- and middle-income countries (LMICs). Several novel RSV prophylactic products are in the pipeline for reducing RSV infections among young infants, including maternal vaccines and immuno-prophylaxis. As these products only provide protection for several months, RSV seasonality needs to be considered when implementing immunisation programmes in order to optimise their use. We searched PubMed for any studies published before 12th May 2020 that assessed the role of RSV seasonality in the effectiveness and efficiency of novel RSV prophylactic programmes for infants in LMICs using the following search formula: ("respiratory syncytial virus" OR RSV) AND (impact OR effective* OR efficien* OR cost-effective*) AND (vaccine OR prophyla* OR antibod* OR immunisation OR immunization). We did not identify any studies that assessed the role of RSV seasonality in the RSV immunisation programmes for LMICs.

Added value of this study

To our knowledge, this is the first study that assessed the impact of passive immunisations of infants with respect to seasonal vs year-round immunisation strategies in LMICs. RSV activity was found to be clearly seasonal in 75% (39/52) of the LMICs. In these LMICs with clear RSV seasonality, seasonal approaches prevented nearly as many RSV cases (effectiveness) and more RSV cases per dose (relative efficiency) compared to year-round administration. Results from multi-year analysis indicated that the effectiveness and relative efficiency of these seasonal approaches could remain relatively stable from year to year if countries applied the same seasonal administration schedules.

Implications of all the available evidence

Our study models head-to-head comparison of the effectiveness and relative efficiency of seasonal vs year-round passive immunisations in LMICs with various RSV seasonality. Our results suggest that seasonal RSV prevention approaches might be considered in some LMICs with clear seasonality, but more information is needed on the cost-effectiveness and programmatic feasibility of seasonal administration.

Introduction

Respiratory syncytial virus (RSV) represents a substantial burden of disease in young children (<5 years), particularly in low- and middle-income countries (LMICs) and in infants <6m.^{1,2} RSV activity is seasonal in most parts of the world and thus poses substantial pressure on health-care services during the seasonal epidemics.³ RSV activity shows a latitudinal gradient in the seasonal onset in each hemisphere; for example, in the northern hemisphere, RSV season usually starts in the late-summer months in the tropics and starts in late- autumn or early-winter months in the temperate areas.^{3,4}

Currently, a number of RSV vaccine candidates and monoclonal antibodies (mAbs) are in late clinical development.⁵ Maternal RSV immunisation grants protection to infants passively by boosting naturally occurring maternally derived antibodies. New long-acting mAbs grant protection to infants by directly injecting antibodies engineered to have extended half-lives (~5m).⁶ A recent cost-effectiveness study based on hypothetical efficacy data suggest that both RSV long-acting mAbs and maternal vaccine can potentially be optimal candidates for Gavi-eligible countries, depending on a country's willingness-to-pay values.⁷

Nonetheless, it should be noted that both maternal immunisation and mAbs will only protect an infant for a limited period (~3–5 months).^{6,8} Therefore, seasonal dosing administration approaches in places with clear seasonality might enhance cost-effectiveness of these prophylaxis strategies. In the present study, we assessed the potential impact of different approaches for administration of mAb and maternal vaccine among LMICs by evaluating the annual and per-dose proportion of RSV-ALRI averted among infants <6m.

Methods

Data sources

We listed countries as LMICs (**Appendix** pp 1–2) based on World Bank Income classification (updated in June 2019).⁹ A total of 52 LMICs with available RSV seasonality data were included in our study. Data on RSV seasonality, burden, immunisation coverage and efficacy were identified and extracted (details in **Appendix** (pp 3–6)).

Briefly, we included RSV seasonality data from our recent systematic review³ and updated the literature search to include studies published between 2018 and 2019 (details in **Appendix** pp 3–5). As our study focuses on the national level impact of RSV prophylaxis, nationwide RSV activity data, where available, were selected to represent the RSV activity for a given country. If no nationwide RSV data were available, the nearest site with RSV activity data to the country's geographical centre

was selected to represent its nationwide RSV activity. For RSV burden data, RSV-ALRI incidence and hospitalisation rates among infants in LMICs were obtained from our previously published RSV global burden estimates.¹

For the immunisation coverage data, we assumed that mAbs were administered at birth, as this was considered a practical option for LMICs, and at the same country-specific coverage as other birth doses (Bacillus Calmette-Guérin (BCG) and hepatitis B vaccines).¹⁰ We assumed that maternal vaccine was administered at the beginning of the third trimester. We used the WHO ANC4+ indicator (defined as the percentage of women aged 15–49 with a live birth who received antenatal care (ANC) four or more times)¹¹ as a proxy for maternal vaccine coverage. We used available efficacy data for the candidate product furthest along in clinical trials – ResVax for maternal immunisation (Novavax)⁸ and Nirsevimab for long-acting mAb (Astra-Zeneca/Sanofi)¹².

Definition for RSV seasonal epidemics

We used the same definition for RSV seasonal epidemics as detailed in our recent study on global RSV seasonality.³ Annual average percentage (AAP), defined as the percentage of the estimated annual RSV incidence that occurred in each month, was calculated to describe the seasonality of RSV for each country. The duration of RSV seasonal epidemics was defined by the minimum number of months that accounted for at least 75% of the annual positive number of RSV cases, with each of these months labelled as an “epidemic month”. An inverse relationship existed between the duration of RSV seasonal epidemics and the degree of RSV seasonality, with shorter duration of RSV seasonal epidemics indicating greater seasonal activity. We defined countries with clear RSV seasonality as those that had ≤ 5 epidemic months in a year. For multi-year RSV activity data, the aforementioned definitions were applied to each year. For countries with clear RSV seasonality, the onset of the RSV season was defined by the first epidemic month of the longest consecutive epidemic months.

Candidate approaches for RSV prophylaxis

For the mAb programme, a total of five candidate approaches were considered, including four seasonal approaches (A–D), and one year-round approach (**Figure 1**). In seasonal approach A, mAbs are administered in each epidemic month, while seasonal approaches B–D begin administration of mAb 1, 2 and 3 months prior to the onset of the first epidemic month, respectively, to protect infants who are born several months before the RSV season but are likely to be exposed to the virus during the RSV season at a very young age when the risk of severe RSV disease is high.

For the maternal vaccine programme, three candidate approaches were considered, including two seasonal approaches (A and B), and one year-round approach (**Figure 2**). Unlike the mAb

programme, the maternal vaccine administration is timed according to the maternal due date, and we did not consider approach C or D for the maternal vaccine due to the likely shorter duration of protection by the maternal vaccine (~90 days) than the mAb (~150 days). More details regarding the seasonal approaches are in the appendix (p7). Note that for each seasonal approach, the number of dosing months (i.e. months in which the administration of RSV prophylaxis needs to be implemented) is country-specific as it depends on the number of epidemic months.

Definitions for effectiveness and relative efficiency

For each candidate approach, we defined effectiveness as the proportion of the total annual RSV-ALRI and RSV-ALRI hospitalisation episodes among infants under six months of age that could be averted. We defined relative efficiency as the ratio of per-dose effectiveness between the seasonal approach and the year-round approach; countries with more seasonal RSV activity are expected to have higher relative efficiency as fewer doses are required to prevent the same proportion of RSV-ALRI / hospitalisation episodes.

Detailed calculations related to effectiveness and relative efficiency can be found in the appendix (p8). All calculations were conducted for each country, each RSV immunisation (i.e. mAb and maternal vaccine), and each RSV outcome (i.e. RSV-ALRI and RSV-ALRI hospitalisation). Briefly, we applied the monthly RSV activity to the annual RSV incidence in each month of age, assuming that RSV seasonality was identical across different months of age. Then for each calendar month, the proportion of RSV episodes was calculated for each month of age (among infants <6m) so all the proportions across calendar months and months of age add up to 100%. Based on the dosing schedules, we identified the group of infants of certain months of age in certain months of a year that could directly benefit from the candidate programme, referred to as “the benefit group” (i.e. the green areas in **Figures 1–2**). Finally, we applied the corresponding efficacy and coverage results to the cumulative incidence among “the benefit group” to calculate the incidence that could be averted. For each approach, interquartile range (IQR) was calculated to present the dispersion of effectiveness and relative efficiency among LMICs with each LMIC as the unit.

In addition, we estimated the proportion of RSV-ALRI outcomes in the first three months of life by each birth month (see p9 for details).

Sensitivity analysis and software

For a subset of LMICs where multi-year RSV activity data were available, we calculated effectiveness and relative efficiency for each year using the same dosing schedule to assess robustness of our results. As a sensitivity analysis, we considered 100% coverage to estimate an upper limit of the potential effectiveness. As protection from both mAb and maternal vaccine might decay

exponentially after birth, we also considered a monthly efficacy decay rate of 0·8 while maintaining the average efficacy consistent with the clinical trial efficacy data. For the maternal vaccine, we ran additional analyses by increasing the duration of protection from 3 months to 5 months and by assuming the same efficacy as mAb (details in **Appendix p10**)

All data analyses were done in the R software (version 3.5.2)¹³ with codes available in GitHub¹⁴. Workflows are described in **Figure S1, Appendix p25**.

Role of the funding source

This work was commissioned by WHO through a grant from the Bill & Melinda Gates Foundation (Global Health Grant OPP1114766). Dr. Daniel Feikin of WHO, was involved in study design, data collection, data interpretation and writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

RSV seasonality in LMICs

A total of 52 LMICs were included in the analysis (**Figure S2, Appendix p25**). Most of these LMICs (39/52, 75%) had clear seasonal RSV activity. Equatorial LMICs tended to have year-round RSV activity. Countries with similar latitudes were more likely to have similar RSV seasonality (**Figure S3, Appendix p26**). Multi-year RSV activity data were available in 25 LMICs. In countries with clear RSV seasonality, RSV onset was within ± 1 month of country's average onset in 74% (113/152) of the years and was within ± 2 months of country's average onset in 89% (135/152) of the years (**Figure S4, Appendix p27**).

Infants born 1–2 months before peak RSV activity had the highest risk of being hospitalised due to RSV-ALRI, as shown by a comparison of the percentage of children born in each month and the peak month of RSV-ALRI hospitalisation (**Figure S5, Appendix p28**). Similar time lags were observed for RSV-ALRI (**Figure S6, Appendix p29**).

Dosing schedule

The median number of mAb dosing months among the 52 LMICs was 4 months (IQR: 3–5) for the seasonal approaches A and B, 6 months (IQR: 4–7) for the seasonal approach C, and 6·5 months (IQR: 5–8) for the seasonal approach D (**Figure S7, Appendix p30**). The median number of maternal vaccine dosing months was 4 months (IQR: 3–6) for the seasonal approaches A and B (**Figure S8, Appendix p31**).

Effectiveness and relative efficiency

We first evaluated effectiveness and relative efficiency across all the 52 countries (**Figure 3**). For mAb, the effectiveness was higher in the year-round approach and the seasonal approach D, followed by the seasonal approach C, and was lower in the seasonal approaches A and B for both outcomes (RSV-ALRI and RSV-ALRI hospitalisation). Relative efficiency was higher in the seasonal approaches B, C and D, followed by the seasonal approach A, and was lowest in the year-round approach for both RSV outcomes. The median effectiveness of the year-round approach for averting RSV-ALRI hospitalisation was 58% (IQR: 51–64) and increased to 66% when assuming 100% coverage (**Table S1, Appendix p11**).

For maternal vaccine, the seasonal approach B had the highest relative efficiency. The median effectiveness of the year-round approach for averting RSV-ALRI hospitalisation was 19% (IQR: 13–21) (**Table S2, Appendix p11**), increasing to 24% when assuming 100% coverage. In sensitivity analyses, year-round effectiveness rose slightly to 21% when assuming five months of protection and to 34% when assuming same efficacy as mAb.

We then assessed the effectiveness and relative efficiency by country (mAb in **Figure 4** and **Figure S9, Appendix p32**; maternal vaccine in **Figures S10–S11, Appendix pp33–34**). For mAb, in countries with an RSV epidemic of ≤ 5 months duration, seasonal approach D was generally favourable with a median relative efficiency of 1.70 (IQR: 1.50–1.97) in preventing RSV-ALRI hospitalisation and only 16% loss of effectiveness (IQR: 13–18) compared to the year-round approach (**Table 1**). As the duration of RSV epidemics increased, the advantages of seasonal approaches became less pronounced and year-round approach became more favourable. Similar findings were observed for maternal immunisation. These results were robust when assuming an efficacy decay of 20% by month (**Tables S3–S4, Appendix p12**).

We lastly assessed the year-to-year variations in the effectiveness and relative efficiency of RSV immunisations, assuming countries adopted fixed dosing schedules based on their average epidemic months. In countries with clear RSV seasonality, seasonal approaches C and D for mAb and seasonal approach B for maternal vaccine had stable efficiency and effectiveness results (**Figures S12–S15, Appendix pp35–38; Tables S5–S10, Appendix pp13–24**).

Discussion

To the best of our knowledge, this is the first study that compared the impact of seasonal programmes and year-round programmes for RSV prophylactic products targeted at infants <6m in LMICs with variable RSV seasonality. RSV activity was clearly seasonal (75% of disease episodes

occurs over ≤ 5 months) in three-quarters of the LMICs. In these LMICs with clear RSV seasonality, seasonal immunisation approaches achieved high relative efficiency and did not lose substantial effectiveness compared to the year-round approach for both mAb and maternal vaccine strategies. Moreover, these results are insensitive to annual variation in RSV seasonality within countries.

As in previous studies on global RSV seasonality,^{3,4} in countries with ≤ 5 RSV epidemic months, a single dose of long-acting passive immunisation or maternal immunisation could protect infants for most of the duration of the peak RSV season. This was supported by the effectiveness and relative efficiency results in the present study among countries with clear RSV seasonality. With a median programme length of 6 months, the mAb approach in which vaccination began 3 months before the RSV season could prevent 49% of the RSV-ALRI hospitalisations among infants < 6 m in these countries. Compared with the year-round approach, this was 70% more efficient by cutting down approximately half of the doses demanded and managing to lose only 16% of the total RSV-ALRI hospitalisations averted by the year-round approach. For the maternal vaccine, with a median programme length of 4 months per year, the optimal seasonal approach could prevent 14% of the RSV-ALRI hospitalisations among infants < 6 m in countries with clear RSV seasonality. Compared with the year-round approach, this approach was 126% more efficient by cutting down almost two-thirds of the doses demanded and managing to lose only 27% of the total RSV-ALRI hospitalisations averted by the year-round approach.

Among all seasonal approaches in the study, it was worth noting that the approaches that advance immunisation by 1–3 months before the onset of RSV seasonal epidemics generally achieved higher effectiveness and relative efficiency than the approach that only administered prophylactic during RSV epidemic months. This finding was similar to the mathematic modelling study in the UK by Cromer et al.¹⁵ Instead of proposing seasonal strategies, Cromer and colleagues applied grid search that went through all combinations of dosing schedules from a one-month programme to a year-round programme and from January to December. They found that the most cost-effective strategy was to protect neonates born in November, one month before the RSV season. In the present study, we found that infants born in 1–2 months before RSV seasonal epidemics in LMICs generally had higher risks of being hospitalised for RSV-ALRI during the first three months of their life (**Figure S5, Appendix p28**). This, in turn, supported the advanced seasonal approaches for immunisation programmes that aim to protect neonates.

Instead of using hypothetical vaccine efficacy data, we applied real-world efficacy data from clinical trials. As no efficacy data were available in terms of the change over time during the period of protection, we assumed the efficacy remained at the same level over time in our main analysis. This

assumption might not hold as efficacy is likely to decay over the first few months of life as antibody level decreases, which would disproportionately affect advanced seasonal approaches because the protection might decay to a lower level when the infants entered the RSV season 1–3 months after birth. Nonetheless, our results from sensitivity analyses using a decay rate of 80% showed little sign of impact on the effectiveness and efficiency results of these advanced seasonal approaches. Another potential limitation of the efficacy data used for this analysis is that these were derived from clinical trials that enrolled participants mostly in high- and upper middle-income countries (albeit in resource poor settings in the latter); efficacy data from low-income populations could improve the validity of this analysis.

While LMICs have a higher burden of RSV-ALRI than high-income countries, most have no ongoing RSV surveillance in order to inform decision making on the RSV immunisation strategy. In this study, we included multi-year RSV data from 25 LMICs and found that for countries with clear RSV seasonality, the onset of RSV season varied by 1 month in most (74%, 113/152) of the years. Similar findings were observed in the early report of the WHO RSV surveillance pilot.¹⁶ The relative stability of RSV season from year-to-year in LMICs with clear RSV seasonality suggest that a few years of surveillance to establish seasonality might be sufficient to establish a fixed seasonal administration program.

Although the use of seasonal approaches for countries with clear RSV seasonality was supported by both mAb and maternal vaccine immunisations, one cannot ignore the relatively low effectiveness of the maternal vaccine in the results of our study. Results from our ad-hoc sensitivity analyses suggest that the efficacy of the maternal vaccine plays a determinant role in the effectiveness of a maternal vaccination programme, which increased by 75% (from 19% to 34%) when applying a higher efficacy (equivalent to mAb). Of note, the vaccine efficacy used for the maternal immunisation approach was based on the first vaccine, ResVax, which failed to reach its primary endpoint;⁸ future trials of maternal immunisation products might result in higher efficacy inputs for this approach. It should also be noted that the relative efficiency results comparing seasonal vs year-round approach are not affected by the input of efficacy data as they were cancelled off in the calculation.

There are some caveats when interpreting the results of this study. First, the coverage data we applied to the analysis might not reflect the real uptake and thus might bias the estimate for effectiveness. For mAb, although the birth dose of BCG vaccine and Hepatitis B vaccine are both likely to be valid proxies, concerns among parents about having another injection to their newborn babies could lead to a lower uptake. For the maternal vaccine, the use of ANC4+ data are likely to underestimate the uptake as pregnant women with four or less ANC visits could still present for an

earlier ANC visit during the eligible vaccination window. Nonetheless, sensitivity analyses assuming 100% coverage suggested that effectiveness was less sensitive to coverage compared to other factors.

Second, we were unable to adjust for different timing of maternal immunisation due to the lack of relevant efficacy data. Earlier immunisation increased maternal vaccine-induced antibodies and was expected to be associated with higher efficacy.¹⁷ As we assumed that all maternal vaccines were administered timely (i.e. in the 28th gestational week), this could lead to a possible underestimate for the effectiveness. This is because the vaccine efficacy data were extracted from the ResVax trial that included mothers who were vaccinated after the 33rd gestational week (thus having lower efficacy than if they were to be vaccinated in the 28th gestational week).⁸ Similarly, we were unable to adjust for the potential impact by preterm delivery on the effectiveness and relative efficiency of maternal immunisation. On the one hand, preterm delivery leads to lower efficacy by reducing the time for the production of vaccine-induced antibodies and for the transfer of these antibodies.^{17,18} Additionally, for the maternal immunisation seasonal approaches, some prematurely born infants might not receive vaccine because their expected date of delivery put them outside of the window for maternal vaccination.

Third, our analysis was conducted at the national level. For geographically large countries or countries with known high spatial variations in RSV season (e.g. Kenya³), regional-specific seasonal programme or national year-round programme might be considered. For twenty-two countries (42% of the included countries) with no available nationwide RSV seasonality data, we used the nearest site with available RSV seasonality data to country's centroid as the best available proxy for nationwide RSV activity, assuming that there was latitudinal/longitudinal gradient in the timing of RSV season onset within each country. This assumption might not hold true and nationwide RSV seasonality data are still needed from these countries to confirm our findings.

Fourth, the RSV seasonality data included in the study were from various sources and their representativeness could vary depending on criteria for testing, respiratory samples, and testing and reporting practices. These data were all collected before the Coronavirus disease 2019 (COVID-19) pandemic.¹⁹ It remains unknown how COVID-19 would impact the seasonality of RSV in the short and medium term (next 3-5 years).

Given the disproportionately high severe RSV disease burden in infants under six months of age in LMICs, it is crucial to consider the introduction of RSV passive immunisations to LMICs as soon as they become available. Our study showed that seasonal dosing approaches in LMICs with clear RSV seasonality might prevent more cases per dose administered compared to year-round

administration. Such approaches might be more cost-effective and feasible in supply-constrained settings. However, more information on the programmatic suitability and acceptability of seasonal approaches is warranted.

Contributor

DF, HN, YL, KA and DH conceptualised the study. YL led the data collection with contribution from XW. YL and DH led the data analysis. HN, YL and DF led the data interpretation. YL wrote the first draft of the report. All authors critically reviewed the report and approved the final draft of the report.

Declaration of interests

YL reports grants from WHO during the conduct of the study, and grants from the Foundation for Influenza Epidemiology outside the submitted work. DH and KA report grants from WHO during the conduct of the study. HN reports grants from WHO during the conduct of the study; grants from the Foundation for Influenza Epidemiology, grants from Innovative Medicines Initiative, grants from the WHO, personal fees from Bill and Melinda Gates Foundation, grants and personal fees from Sanofi, grants from National Institute of Health Research, personal fees from Janssen and personal fees from AbbVie, outside the submitted work. All other authors have nothing to declare.

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Figures (attached separately)

Figure 1. Schematic figure presenting the candidate approaches for monoclonal antibodies

Figure 2. Schematic figure presenting the candidate approaches for maternal immunisation

Figure 3. Results of effectiveness and relative efficiency for monoclonal antibodies and maternal immunisation in LMICs. Each point represents a country. Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach.

Figure 4. Country-specific results of effectiveness and relative efficiency in averting RSV-ALRI hospitalisations for monoclonal antibodies. Number after each country indicates duration of RSV epidemics (in months). Effectiveness is defined by annual proportion averted among infants under six months of age; relative efficiency is defined by the ratio between per-dose effectiveness of a seasonal approach and that of the year-round approach. Approaches in the upper right quadrant would be considered those with optimal effectiveness and relative efficiency.

1 **Table 1.** Effectiveness and relative efficiency results for each candidate approach among countries with ≤5 epidemic months

Approach	Dose months	RSV-ALRI			RSV-ALRI hospitalisation		
		Effectiveness	Effectiveness ratio*	Relative efficiency	Effectiveness	Effectiveness ratio*	Relative efficiency
<u>Monoclonal antibody</u>							
Seasonal A	4 (3–5)	18·1 (14·5–21·9)	0·39 (0·32–0·46)	1·19 (1·09–1·30)	25·8 (20·3–30·7)	0·45 (0·37–0·53)	1·36 (1·24–1·54)
Seasonal B	4 (3–5)	22·3 (19·3–28·0)	0·48 (0·40–0·59)	1·55 (1·46–1·70)	33·0 (28·2–39·0)	0·58 (0·51–0·65)	1·83 (1·65–2·10)
Seasonal C	5 (4–6)	32·1 (26·9–36·2)	0·68 (0·60–0·73)	1·69 (1·52–1·80)	42·4 (36·4–48·0)	0·75 (0·70–0·78)	1·82 (1·60–2·09)
Seasonal D	6 (5–7)	38·6 (34·7–42·9)	0·82 (0·79–0·84)	1·65 (1·46–1·89)	49·4 (44·3–53·8)	0·84 (0·82–0·87)	1·70 (1·50–1·97)
Year-round	12 (12–12)	49·1 (42·2–52·5)	1 (Reference)	1 (Reference)	59·9 (51·5–64·1)	1 (Reference)	1 (Reference)
<u>Maternal vaccine</u>							
Seasonal A	4 (3–5)	6·8 (5·2–7·7)	0·66 (0·59–0·70)	2·03 (1·79–2·40)	11·1 (7·8–13·7)	0·60 (0·51–0·67)	1·82 (1·69–2·07)
Seasonal B	4 (3–5)	7·1 (5·3–8·2)	0·7 (0·64–0·75)	2·22 (1·85–2·69)	13·7 (10·6–15·8)	0·73 (0·67–0·75)	2·26 (1·87–2·77)
Year-round	12 (12–12)	10·4 (8·8–11·2)	1 (Reference)	1 (Reference)	19·6 (16·4–21·0)	1 (Reference)	1 (Reference)

2 *Effectiveness ratio is calculated by the ratio between the effectiveness of seasonal approach and that of the year-round approach. Results are presented
3 as median (IQR) among the included countries.